US-PAT-NO: **6454811**

DOCUMENT-IDENTIFIER: US 6454811 B1

TITLE: Composites for tissue regeneration and methods of manufacture thereof

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US Patent No. - PN (1):
6454811

Brief Summary Text - BSTX (14):

It has been further recognized that not only the morphology of such devices but the materials of which they are composed will contribute to the regeneration processes as well as the mechanical strength of the device. For example, some materials are **osteogenic** and stimulate the growth of bone forming cells; some materials are osteoconductive, encouraging bone-forming cell migration and incorporation; and some are osteoinductive, inducing the differentiation of mesenchymal stem cells into osteoblasts. Materials which have been found to be **osteogenic** usually contain a natural or synthetic source of calcium phosphate. Osteoinductive materials include molecules derived from members of the transforming growth factor-beta (TGF-beta) gene superfamily including: bone morphogenetic proteins (BMPs) and insulin-like growth factors (IGFs).

Brief Summary Text - BSTX (24):

In one embodiment for repair or replacement of bone, a gradient is formed of **osteogenic** and osteoconductive materials, such as calcium phosphates, to materials which are synthetic biocompatible polymers, such as poly(alpha)esters, which are particularly well suited for attachment of cells and controlled biodegradation. In another embodiment, the devices have a gradient in macroarchitecture. The macroarchitecture, or overall shape, can be of a design which allows fluid flow through and/or around one region and a different shape in another region with a gradient from one shape to the other. In another embodiment, the microarchitecture may be from an osteoinductive system of interconnected pores to a system of staggered channels inductive to

chondrocyte colonization. In another aspect, the gradient may relate to mechanical properties such as tensile or compressive strength. The gradient of properties may be from that which is suitable for weight bearing loads to one which is suitable for soft tissue regeneration.

Claims Text - CLTX (5):

5. The device of claim 1 wherein at least one region or a gradient within a region comprises **osteogenic,** osteoinductive, and/or osteoconductive materials.

US-PAT-NO: **4553272**

DOCUMENT-IDENTIFIER: US 4553272 A
See image for Certificate of Correction

TITLE: Regeneration of living tissues by growth of isolated cells in porous implant and product thereof

---------- KWIC ---------

US Patent No. - PN (1):
4553272

Brief Summary Text - BSTX (7):
It has also been known to use transplantation of cadaveric or animal joints. These attempts have generally been unsuccessful as a result of inadequate revascularization of the implanted joints and immunologic rejection of the **allografts** or zenografts.

DOCUMENT-IDENTIFIER: US 20030049329 A1

TITLE: Method of preparing a poorly crystalline calcium phosphate and methods of its use

---------- KWIC ---------

Detail Description Paragraph - DETX (174):

[0227] Medical Uses of Pellets. The solid PCA calcium phosphate material can be used in many different applications, depending on the details of the situation. The first application applies to orthopedic implants. Pellets, plates, screws, **granules, bone void** fillers and other forms are appropriate for orthopedic applications. The pellets, plates, and screws can be of various shapes and sizes.

DOCUMENT-IDENTIFIER: US 20030036800 A1

TITLE: Composite bone material implant and method

---------- KWIC ---------

Detail Description Paragraph - DETX (58):

[0111] Therefore, one embodiment of the present invention is an osteoinductive bone tissue composite that comprises ground bone tissue molded to form a desired shape; and a cyanoacrylate binder. Furthermore, the composite comprises random "**voids**". The **voids** are spaces between adjacent **bone particles,** and are present both at the surface of a composite as well as within the interior of the composite. These **voids** or spaces vary in size and shape and have a width of up to about 1,000 microns. Preferably the width of the **void** is from about 50-700 microns, more preferably from about 200-500 microns.

Detail Description Paragraph - DETX (61):

[0114] The **voids** exist as a result of the process of the present invention, and their existence promote osteoconductivity of the composite. Without being bound by theory, the **voids** promote osteoconductivity because an influx of undifferentiated mesenchymal cells normally found within osseous structures as well as undifferentiated cells that migrate to the repair site to fill the **voids**. The action of the osteoinductive properties of the composite induce the undifferentiated cells to differentiate into bone-forming cells that both form bone within the **voids** as well as remodel the **bone particles** of the composite matrix into living host bone.

Detail Description Paragraph - DETX (64):

[0117] Now turning to the remaining drawings, FIG. 2 is a cross-section of an embodiment of a composite 50 of the present invention. The **bone particles** 55 are bordered in places by **voids** 60. The **voids** 60 join to form canals 65. Also shown in FIG. 2 are surface **voids** 62. FIG. 3 is a magnified (6.25.times.) photograph of a composite of the present invention. FIG. 4 is a magnified (85.times.) photograph of a composite of the present invention. The **voids,** canals, and **bone particles** described herein are visible.

DOCUMENT-IDENTIFIER: US 20020035401 A1

TITLE: Osteogenic implants derived from bone

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Abstract Paragraph - ABTX (1):

An osteogenic osteoimplant in the form of a flexible sheet comprising a coherent mass of **bone-derived particles, the osteoimplant having a void** volume not greater than about 32% and a method of making an osteogenic osteoimplant having not greater than about 32% **void** volume, the method comprising: providing a coherent mass of **bone-derived particles**; and, mechanically shaping the coherent mass of **bone-derived particles** to form an osteogenic osteoimplant in the form of a flexible sheet.

Summary of Invention Paragraph - BSTX (24):

[0022] In keeping with these and related objects of this invention, there is provided an osteogenic osteoimplant in the form of a flexible sheet having not greater than about 37% **void** volume comprising a coherent mass of **bone-derived particles**. This is in contrast to the shaped materials prepared in accordance with U.S. Pat. No. 5,507,813 that have a **void** volume of at least about 37% and the load-bearing materials prepared in accordance with U.S. patent application Ser. No. 09/256,447 filed Feb. 23, 1997 which have a wet compressive strength of at least about 3 MPa.

Detail Description Paragraph - DETX (51):

[0092] Turning now to the figures. FIG. 1 is a cross-sectional view of a shaped material prepared according to U.S. Pat. No. 5,507,813. The section is stained to show the presence of **bone particles** and powder as well as **void** space. The dark areas of the figure are stained bone material, the white area is the **void** space contained within the shaped material. FIG. 2 is a cross-sectional view of an osteogenic osteoimplant prepared as described in example 2 herein and stained in the same manner as FIG. 1. A comparison of FIG. 2 with FIG. 1 reveals that the osteoimplant of the invention herein has 42% less **void** space than the material of FIG. 1. The lesser **void** space proceeds partially from the greater packing efficiency achieved through the use

of small **bone particles** to fill the spaces left between the larger elongate particles as well as the force(s) applied in the forming of the osteogenic osteoimplant.

Claims Text - CLTX (2):

1. An osteogenic osteoimplant in the form of a flexible sheet comprising a coherent mass of **bone-derived particles,** the coherent mass formed at least in part from elongate bone-derived elements optionally in combination with **bone powder, the osteoimplant** possessing an average **void** volume of not greater than about 32%.

Claims Text - CLTX (15):

14. A method of forming an osteogenic osteoimplant having not greater than about 32% **void** volume, the method comprising: providing a coherent mass of **bone particles** optionally in combination with one or more biocompatible components, the coherent mass formed at least in part from elongate bone-derived elements optionally in combination with **bone powder**; and, mechanically shaping the coherent mass of **bone particles** to form the osteogenic osteoimplant.

Claims Text - CLTX (34):

33. An osteoimplant comprising a mechanically shaped composition of elongate **bone particles** selected from the group consisting of nondemineralized **bone particles, demineralized bone particles,** and combinations thereof, wherein the osteoimplant possesses a **void** volume not greater than about 32%.

US-PAT-NO: 6180606

DOCUMENT-IDENTIFIER: US 6180606 B1

TITLE: Compositions with enhanced osteogenic potential, methods for making the same and uses thereof

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Brief Summary Text - BSTX (49):

By way of example, the growth factor TGF-.beta. can be present on or within the collagen matrix of the collagen demineralized bone osteogenic composition which has the form of a sponge. Preferably, the growth factor TGF-.beta.2 is used. The TGF-.beta.2 may be natural or synthetic in origin. The TGF-.beta.2 is contacted with the sponge allowing the growth factor to be located on or within the matrix and **void** volume of the porous or semi-porous structure of the sponge. Alternatively, the TGF-.beta.2 is contacted with the osteogenic factor allowing the growth factor to be located on or within the osteogenic factor. The amount of the TGF-.beta.2 added to the sponge and/or osteogenic factor can range from nanogram to milligram quantities. A preferred amount of TGF-.beta.2 to be added is about 0.1 ng to 500 mg, more preferred is about 10 ng to 100 mg, and most preferable is about 100 ng to 5 mg per 40 to 80 mg of sponge. By way of example, a collagen-demineralized bone osteogenic sponge comprising 75% collagen and 25% demineralized **bone powder** (weight ratio), may have added on or within the matrix and/or osteoginductive factor, about 5 .mu.g of TGF-.beta.2 per 40 mg of sponge or per 80 mg of sponge.

US-PAT-NO: 6180605

DOCUMENT-IDENTIFIER: US 6180605 B1

TITLE: Composition with enhanced osteogenic potential, method for making the same and therapeutic uses thereof

---------- KWIC ---------

Brief Summary Text - BSTX (24):

In one embodiment, this invention provides improved osteogenic composition for use as implants comprising a matrix of collagen complexed with demineralized **bone particles,** BMP, BMPs or combinations thereof to which is added, by sorption onto or into the porous or semi-porous matrix structure, an aqueous solution containing one or more soluble growth factors. The collagen matrix complexed with the osteogenic factor to which the soluble growth factor is to be sorbed, may also be in the form of a semi-porous or porous sponge, (Jefferies U.S. Pat. Nos. 4,394,370 and 4,472,840) a membrane, a fiber-like structure, powder, fleece, particles or fibers. The growth factor or factors may be delivered to the collagen demineralized bone compositions in a liquid form, but can be provided in a dry state prior to reconstitution and administrated by sorption onto or into the collagen-demineralized bone or BMP compositions. One of skill in the art will appreciate that the growth factor is sorbed onto or into the matrix and may also reside within the **void** volume of the porous or semi porous matrix.

Brief Summary Text - BSTX (25):

By way of example, the growth factor TGF-.beta. can be sorbed into or onto the collagen matrix of the collagen demineralized bone osteogenic composition in the form of a sponge. Preferably, the growth factor TGF-.beta.2 is used. The TGF-.beta.2 may be natural or synthetic in origin. The TGF-.beta.2 is contacted with the sponge allowing the growth factor to be sorbed onto or into the matrix and **void** volume of the porous or semi-porous structure of the sponge. The amount of the TGF-.beta.2 sorbed onto the sponge can range from nanogram to milligram quantities. Preferred amount of TGF-.beta.2 to be sorbed are about 0.1 ng to 500 mg per 40 to 80 mg of sponge, most preferred is about 10 ng to 100 mg and most preferable is about 100 ng to 5 mg. By way of example, a collagen-demineralized bone osteogenic sponge comprising 75 collagen

and 25% demineralized **b ne powder** (weight ratio) may have sorbed onto or into the matrix about 5 ug of TGF-.beta.2 per 40 mg of sponge or per 80 mg of sponge.

DOCUMENT-IDENTIFIER: US 20030036800 A1

TITLE: Composite bone material implant and method

---------- KWIC ---------

Summary of Invention Paragraph - BSTX (8):

[0007] Until recently, developers of bone transplants and prostheses have believed that it is desirable to maintain graft tissue in a living state during the grafting process. It is relatively undisputed that the use of living tissue in a graft will promote bone healing, but recent surgical experience has shown that healing can be achieved with **allografts** of non-living bone material which has been processed.

Summary of Invention Paragraph - BSTX (9):

[0008] Processing of bone material which does not contain living tissue is becoming more and more important. Non-living bone grafting techniques have been attempted both for autografts and for **allografts**. The use of autograft bone is where the patient provides the source of the bone, and the use of **allograft** bone is where another individual of the same species provides the source of the bone.

Summary of Invention Paragraph - BSTX (13):

[0012] It is now possible to obtain **allograft** bone which has been processed to remove all living material which could present a tissue rejection problem or an infection problem. Such processed material retains much of the mineral quality of the original living bone, rendering it more osteoinductive. Moreover, it can be shaped according to known and new methods to attain enhanced structural behavior. In fact spine surgeons express a distinct preference for such materials, and at least one supplier, the Musculoskeletal Transplant Foundation (MTF), has introduced femoral ring **allografts** for spine surgeries.

Summary of Invention Paragraph - BSTX (14):

[0013] Research shows that such **allografts** are very favorable for spinal surgery. According to Brantigan, J. W., Cunningham, B. W., Warden, K., McAfee,

P. C., and Steffee, A. D., A compression Strength of Donor Bone for Posterior Lumbar Interbody Fusion, Spine, Vol. 18, No. 9, pp.12113-21 (July 1993):

Summary of Invention Paragraph - BSTX (15):

[0014] Many authors have viewed donor bone as the equivalent of autologous bone. Nasca, et al . . . compared spinal fusions in 62 patients with autologous bone and 90 patients with cryopreserved bone and found successful arthrodesis in 87% of autologous and 86.6% of **allograft** patients. (Citations omitted.).

Summary of Invention Paragraph - BSTX (16):

[0015] A drawback of fabricating transplants and prostheses from donated **allograft** is that the process necessitates discard of a great deal of scrap and **powdered bone** material. Good quality donated bone is a scarce resource, so that devising a method of using scrap and **powdered allograft bone** material would be of great assistance to this highly beneficial endeavor. The present invention uses ground bone to make solid shapes. The results of the present invention are superior to the prior art processes and the process and composite of the present invention allows for a greater amount of donor bone to become available. For example, with the present invention, bone can now be used from older donors. With a transplanted **allograft,** older bone may be too brittle and weak.

Summary of Invention Paragraph - BSTX (18):

[0017] Additionally, prior art techniques have a serious limitation in that bone parts and bone products made from **allograft** cortical tissue may be limited in size, dimension and shape because of the anatomical limits on the thickness and length of the source bone. With the method of the present invention, many shapes and forms can be fabricated from **allograft** cortical bone tissue including pins, screws, plates, intervertebral discs, and the like for use in surgery.

Summary of Invention Paragraph - BSTX (19):

[0018] **Allograft** bone occurs in two basic forms: cancellous bone (also referred to as trabecular bone) and cortical bone. Cortical bone is highly dense and has a compound structure comprised of calcium hydroxyapatite reinforced with collagen fiber. In the present invention, cortical bone tissue is preferred.

Summary of Invention Paragraph - BSTX (20):

[0019] Compression of **allograft** bone is desirable from general considerations. Generally, bone samples are stronger when they are more dense. Compressing **allograft** bone increases its density and thus generally strengthens the **allograft**. In addition, recent studies have indicated that the shell of vertebral bone is very much like condensed trabecular bone. Mosekilde, L., A Vertebral structure and strength in vivo and in vitro, Calc. Tissue Int. 1993;53 (Suppl):121-6; Silva, M. J., Wang, C., Keaveny, T. M., and Hayes, W. C., A Direct and computed tomography thickness measurements of the human lumbar vertebral shell and endplate, Bone 1994:15:409-14; Vesterby, A., Mosekilde, L., Gunderson, H. J. G., et al., Biologically meaningful determinants of the in vitro strength of lumbar vertebrae, Bone 1991; 12:219-24.

Summary of Invention Paragraph - BSTX (21):

[0020] Compression also allows conversion of larger irregular shapes into the desirable smaller shape, thereby permitting more disparate sources of **allograft** bone to be used. By compressing bone to a given shape it is possible to configure the **allograft** to match a preformed donee site prepared by using a shaped cutter to cut a precisely matching cut space. In particular, this method of formation facilitates the formation of match mated surfaces of the implant for the formation of a particular shape for skeletal repair or revision.

Summary of Invention Paragraph - BSTX (23):

[0022] It is known that **allograft** bone can be reshaped into one of many configurations for use as an implant. Various methods, including that of Bonutti, U.S. Pat. Nos. 5,662,710 and 5,545,222, can be used to shape **allograft** material into the desired shape.

Summary of Invention Paragraph - BSTX (24):

[0023] A goal of a bone composite transplant is that the transplant is readily received and hosted by the receiving mammal, with bone fusion occuring (i.e., the composite should be biocompatible and osteoinductive). Today, the only other osteoinductive implants are **allograft** shapes that have been cut and shaped from cadaver donated bone. This method has serious drawbacks in that it is difficult for sufficient fusion to take place and the implant usually lacks sufficient structural strength and density.

Summary of Invention Paragraph - BSTX (25):

[0024] U.S. Pat. No. 6,025,538 to Yaccarino, III, discloses **allograft** bone devices for surgical implantation in the bone tissue.

Summary of Invention Paragraph - BSTX (28):

[0027] U.S. Pat. No. 5,899,939 to Boyce et al. discloses a bone-derived implant that comprises cortical bone and is used to repair, replace, or augment various portions of animal and human skeletal systems. The bone implant of this invention is made up as individual layers that may be held together by adhesives. Finally, the bone-derived implant of this invention may have one or more cavities which may be filed with demineralized **bone powder**. This patent fails to disclose making an implant or prosthesis from ground **bone powder**.

Summary of Invention Paragraph - BSTX (29):

[0028] U.S. Pat. No. 6,025,538 to Yaccarino, III discloses **allograft** bone devices for surgical implantation in the bone tissue. The device is larger than the natural dimensions of a cortical bone layer and is made by combining two or more smaller pieces to form a compound bone structure. A pin may be placed through the component bone members of the bone structure. Finally, each bone member is shaped to form a groove to receive the end of the other bone member. The device of this invention may be processed to form compound bone pins, bone screws, plates, disks, wedges, blocks, etc. The devices may be secured together by using any surgical bone adhesive with a synthetic absorbable or non-absorbable polymer in connection with the pin that connects the two bone pieces together.

Summary of Invention Paragraph - BSTX (31):

[0030] U.S. Pat. No. 6,045,554 to Grooms et al. discloses an interference screw manufactured from cortical **allograft** bone tissue may be used as a fixation screw for cruciate ligament graphs. The screw is made by obtaining a fragment of bone from the cortex and machining the thread, tip and drive head of the screw. More specifically, the section is removed from a femur or tibia, a dowel of the tissue is machined. The machining may be done by a grinding wheel.

Summary of Invention Paragraph - BSTX (32):

[0031] U.S. Pat. No. 5,507,813 to Dowd et al. discloses a process for making surgically implantable materials fabricated from elongate **bone particles**. The particles may be graded into different sizes. Additionally,

the particles are described as filaments, fibers, threads, slender or narrow strips, etc. The elongate **bone particles** may be mixed with an adhesive and/or filler. The fillers include **bone powder**.

Summary of Invention Paragraph - BSTX (33):

[0032] U.S. Pat. No. 5,061,286 to Lyle discloses an osteoprosthetic implant with demineralized **bone powder** attached thereto. The **bone powder** apparently provides an osteogenic coating for the prosthesis. This coating allows the prosthesis to be firmly anchored to the bone repair site. The prosthesis device may be polymeric. The **bone particles** may be adhere to the prosthetic device and each other by a binder. Cyanoacrylate is disclosed as one of the binders.

Summary of Invention Paragraph - BSTX (36):

[0035] U.S. Pat. No. 6,294,187 to Boyce, et al. discloses an osteoimplant for use in the repair, replacement, and/or augmentation of various portions of animal or human skeletal systems. The implant of this patent comprises **bone particles** in combination with one or more biocompatible components. The implant is made by applying compressive force of at least 1,000 psi to the composition.

Summary of Invention Paragraph - BSTX (37):

[0036] U.S. Pat. No. 5,565,502 to Glimcher, et al. discloses a process for removing and isolating the calcium-phosphate crystals of bone. The **bone powder** is prepared by milling bone in liquid nitrogen and sieving to a particle size ranging up to approximately 20 microns. The **bone particles** are then suspended in an organic solvent. The purified calcium-phosphate crystals are isolated from the bone and are useful as an aid to induce and promote bone healing.

Summary of Invention Paragraph - BSTX (38):

[0037] U.S. Pat. No. 5,824,078 to Nelson, et al. discloses an **allograft** bone press. The bone press is used to compress cancellous bone chips to conform to a shape of a mold.

Summary of Invention Paragraph - BSTX (42):

[0041] In response to the need for a composite material to make use of bone fragments and **bone powder** for fabricating implants and prosthetic devices for bone the current inventor developed the present invention.

Summary of Invention Paragraph - BSTX (45):

[0043] Another object of the current invention is to provide a composite material utilizing **bone powder** and/or fragments as well as a method to manufacture and shape the composite into usable implants and/or bone prostheses. In preferred embodiments of the present invention, composite formed from the method of the present invention is of sufficient strength in a body fluid environment to enable the osteoimplant to bear loads.

Summary of Invention Paragraph - BSTX (49):

[0047] More preferably, the bone tissue is greater than about 50% cortical bone tissue, more preferably in the range of greater than about 50-70% cortical bone tissue, more preferably in the range of greater than about 50-90% cortical bone tissue, more preferably in the range of greater than about 50-95% cortical bone tissue, more preferably 90% cortical bone tissue, and more preferably greater than about 95% cortical bone tissue. The size of the ground **bone particles** can vary, but typically the particles will range in size from 125 to 850 microns in size.

Detail Description Paragraph - DETX (59):

[0112] Preferably, the voids are present from about 5% to 50% (by volume of the composite). More preferably, the voids are present from about 15% to 35% (by **volume), and more preferably, the voids** are present in an about of about 25% (by volume).

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	Document ID	Title
5	US 20030049328 A1	Porous beta-tricalcium phospl
6	US 20030045943 A1	Device for regeneration of arti
7	US 20030036800 A1	Composite bone material imp
8	US 20030032098 A1	Bone morphogenic protein

[0037] U.S. Pat. No. 5,824,078 to Nelson, et al. discloses an allograft bone press. The bone press is used to compress cancellous bone chips to conform to a shape of a mold.

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2):

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US 20030036800A1

(19) **United States**

(12) **Patent Application Publication** (10) Pub. No.: US 2003/0036800 A1

Meredith (43) Pub. Date: Feb. 20, 2003

(54) **COMPOSITE BONE MATERIAL IMPLANT AND METHOD**

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(21) Appl. No.: 10/128,219

(22) Filed: Apr. 23, 2002

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/615,643, filed on Jul. 13, 2000.

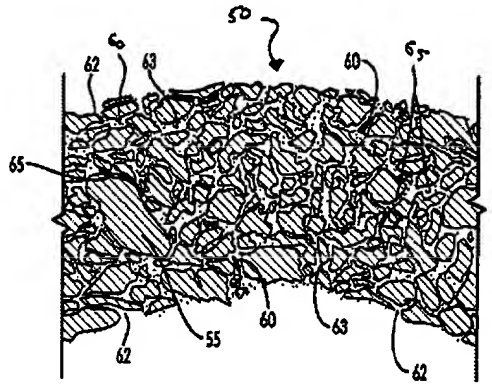
Publication Classification

(51) Int. Cl.[7] A61F 2/28

(52) U.S. Cl. 623/23.63; 264/128; 264/330; 264/571

(57) **ABSTRACT**

The present invention relates to a method of forming a bone composite, comprising: providing bone tissue; grinding said bone tissue to form ground tissue; molding the ground bone tissue into a bone composite; applying a binder to the bone composite; applying a vacuum to the mold, and optionally milling or refining the bone composite to its desired shape. The present invention also encompasses bone tissue composites made therefrom. The composites may be, for example, a bone pin, screw, or prosthesis.



US-PAT-NO: 6454811

DOCUMENT-IDENTIFIER: US 6454811 B1

TITLE: Composites for tissue regeneration and methods of manufacture thereof

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Detailed Description Text - DETX (70):

The two designs having the highest number of positive features are the hollow cylinder and the clover design, both of which can be fabricated with masks. The honeycomb design is another candidate for fabrication using inkjet printheads for drop-on-demand of organic solvents. The honeycomb design enables maximizing both surface area and **void volume** for tissue ingrowth and biological interaction while maintaining high uniaxial strength.

Detailed Description Text - DETX (109):

Results suggest that the 35% NaCl devices were fully leached after the seven-hour period; however, NaCl remained in the 45% NaCl devices even after seven hours of leaching. In both bone device batches, the **void volume** remained relatively constant during the entire leaching duration, with the final residual level being around 13%. This was an unexpected observation, considering water should have displaced all air and NaCl for leaching to be complete. Trapped air pockets may have been present in the samples. This may explain why some devices, such as the cartilage batches, float during leaching even though the densities of the polymer (1.3 g/cm.sup.3) and NaCl (2.17 g/cm.sup.3) are greater than that of water (1.0 g/cm.sup.3).

Claims Text - CLTX (28):

28. The device of claim 27 wherein the non-polymeric particles are selected from the group consisting of **bone particles,** hydroxyapatite particles, and calcium phosphate particles.

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	Document ID	Title
22	US 6331445 B1	Protein-induced morphogenesi
23	US 6492327 B2	Isolation of purified TGF- .be
24	US 6454811 B1	Composites for tissue regener
25	US 6426332 B1	Matrix-free osteogenic device

US-PAT-NO: 6454811

DOCUMENT-IDENTIFIER: US 6454811 B1

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28. The device of claim 27 wherein the non-polymeric particles are selected from the group consisting of bone particles, hydroxyapatite particles, and

US006454811B1

(12) **United States Patent**
Sherwood et al.

(10) **Patent No.: US 6,454,811 B1**
(45) **Date of Patent: Sep. 24, 2002**

(54) **COMPOSITES FOR TISSUE REGENERATION AND METHODS OF MANUFACTURE THEREOF**

(75) Inventors: **Jill E. Sherwood**, Princeton, NJ (US); **Linda G. Griffith**, Cambridge, MA (US); **Scott Brown**, Princeton, NJ (US)

(73) Assignees: **Massachusetts Institute of Technology**, Cambridge, MA (US); **Therics, Inc.**, Princeton, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 09/416,346

(22) Filed: **Oct. 12, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/103,853, filed on Oct. 12, 1998.

(51) Int. Cl.[7] A61F 2/02

(52) U.S. Cl. 623/23.76; 623/23.72

(58) **Field of Search** 623/23.76, 17

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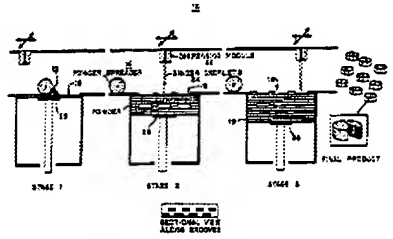
(57) **ABSTRACT**

Composite devices for tissue engineering are provided having a gradient of one or more of the following: materials, macroarchitecture, microarchitecture, or mechanical properties, which can be used to select or promote attachment of specific cell types on and in the devices prior to and/or after implantation. In various embodiments, the gradient forms a transition zone in the device from a region composed of materials or having properties best suited for one type of tissue to a region composed of materials or having properties suited for a different type of tissue. The devices are made in a continuous process that imparts structural integrity as well as a unique gradient of materials in the architecture. The gradient may relate to the materials, the macroarchitecture, the microarchitecture, the mechanical properties of the device, or several of these together. The devices disclosed herein typically are made using solid free form processes, especially three-dimensional printing process (3DP™). The device can be manufactured in a single continuous process such that the transition from one layer of tissue regeneration scaffold and the other layer of tissue regeneration scaffold have no "seams" and are not subject to differential swelling along an axis once the device is implanted into physiological fluid.

62 Claims, 4 Drawing Sheets



US-PAT-NO: 4553272

DOCUMENT-IDENTIFIER: US 4553272 A
See image for Certificate of Correction

TITLE: Regeneration of living tissues by growth of isolated cells in porous implant and product thereof

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Brief Summary Text - BSTX (9):

U.S. Pat. No. 2,621,145 discloses a flexible strip of **particles of bone** held together by a fibrin network positioned on a carrier strip of a material such as cellophane. This is said to encourage rapid regrowth of bone by the body. The material, however, does not have the mechanical strength to permit replacement of a structural portion of the body therewith. It also lacks an isoelastic substrate for effective restitution of biological matrix.

Detailed Description Text - DETX (6):

The implant pores which receive the daughter cells and contain the tissue grown therewithin during culturing and thereafter, preferably have a pore size on the order of 25 to 75 microns with 50 to 70 microns being the preferred range. On a **volume basis, it is preferred that the pore** openings be about 20 to 50 percent of the of the total implant volume with about 30 to 40 percent being the preferred volume relationship. It is generally desirable to effect a balance between desired strength and porosity. For some uses where the site of attachment is adjacent to bone, the implant may be provided with another series of pores which are larger and may be about 100 to 400 microns in size. These larger pores serve to permit ingrowth of blood vessels and adjacent osteogenic cells after implantation in the patient. Where both pore sizes are provided, it is preferred to establish a barrier between the two pore sizes so as to resist undesired commingling of the tissue generated by the daughter cells with the blood vessels and osteogenic cells which are ingrown in the patient.

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	Document ID	Title
46	US 5108436 A	Implant fixation
47	US 4888366 A	Inductive collagen-based bone
48	US 4553272 A	Regeneration of living tissues

TITLE: Regeneration of living tissues by growth of isolated cells in porous implant and product thereof

KWIC

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United States Patent [19]

Mears

[11] Patent Number: 4,553,272

[45] Date of Patent: Nov. 19, 1985

[54] REGENERATION OF LIVING TISSUES BY GROWTH OF ISOLATED CELLS IN POROUS IMPLANT AND PRODUCT THEREOF

[75] Inventor: Dane C. Mears, Oakmont, Pa.

[73] Assignee: University of Pittsburgh, Pittsburgh, Pa.

[21] Appl. No.: 238,274

[22] Filed: Feb. 26, 1981

[51] Int. Cl.⁴ A61F 1/00

[52] U.S. Cl. ..... 623/1; 128/92 C; 128/92 G; 623/10; 623/16

[58] Field of Search ..... 128/92 G; 3/1.9, 1

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Assistant Examiner—David Isabella

Attorney, Agent, or Firm—Arnold B. Silverman

[57] ABSTRACT

A method of repair of patient tissues by implant including providing a living cell sample which is introduced into an implant member having a porous open structure. The cell sample may be cultured in the implant. The implant is secured to the patient, as by surgical implantation. In one embodiment, the implant portion which receives the cells preferably has a pore size of about 25 to 75 microns. In addition, a second pore size of about 100 to 400 microns for receipt of blood vessels and osteogenic cells through ingrowth after introduction into the patient, may be provided. The cell sample may advantageously be selected from the group consisting of cartilage cells, tendon cells, ligament cells and musculotendinous cells. The implant member may be advantageously used in bone or joint reconstruction surgery and in other forms such as artificial tooth implantation.

A surgical implant comprising an inert member having, in one embodiment, a first series of open pores of an average size of about 25 to 75 microns and a second series of open pores of an average size of about 100 to 400 microns with patient cells growing within the pores.

3 Claims, 6 Drawing Figures